The Effect of Exercise on the Absorption of Inhaled Human Insulin via the AERx Insulin Diabetes Management System in People With Type 1 Diabetes

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OBJECTIVE — This study investigated the effect of moderate exercise on the absorption of inhaled insulin via the AERx insulin diabetes management system (iDMS).

RESEARCH DESIGN AND METHODS — In this randomized, open-label, four-period, crossover, glucose clamp study 23 nonsmoking subjects with type 1 diabetes received a dose of 0.19 units/kg inhaled human insulin followed in random order by either *1*) no exercise (NOEX group) or 30 min exercise starting, *2*) 30 min after dosing (EX30), *3*) 120 min after dosing (EX120), or *4*) 240 min after dosing (EX240).

RESULTS — Exercise changed the shape of the free plasma insulin curves, but compared with the NOEX group the area under the curve for free plasma insulin (AUC_{ins}) for the first 2 h after the start of exercise was unchanged for EX30 and EX240, while it was 15% decreased for EX120 ($P < 0.01$). The overall insulin absorption during 6 and 10 h after dosing was 13% decreased for EX30 ($P < 0.005$), 11% decreased for EX120 ($P < 0.01$), and unchanged for EX240. Exercise did not influence the maximum insulin concentration (C_{max}), while the time to C_{max} was 22 min earlier for EX30 ($P = 0.04$). The AUC for the glucose infusion rate (AUC_{GIR}) for 2 h after the start of exercise increased by 58% for EX30, 45% for EX120, and 71% for EX240 (all $P < 0.02$) compared with the NOEX group.

CONCLUSIONS — Thirty minutes of moderate exercise led to unchanged or decreased absorption of inhaled insulin via AERx iDMS and faster C_{max} for early exercise. Thus, patients using AERx iDMS can adjust insulin dose as usual independent of time of exercise, but they should be aware of the faster effect if exercising early after dosing.

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Ever since the introduction of insulin injections 80 years ago, alternatives to injections of insulin have been sought after (1,2). Today, inhaled human insulin is an alternative to injected mealtime insulin, with the first product on the market and several systems in development (3). The AERx insulin diabetes management system (iDMS) (insulin inhaler and disposable insulin strips) is one such system and is currently under development by Novo Nordisk (Bagsvaerd, Denmark). The system allows dose adjustment in single-unit increments and ensures delivery of inhaled insulin to the deep lung by means of electronically controlled release of a fine-particle insulin aerosol only when the inspiratory flow rate and inhaled volume of the user are optimal for deep-lung delivery (breath check) (4).

Numerous studies have been performed with inhaled insulin over the last 10 years, investigating, among others, the effect of smoking (5,6), upper respiratory tract infection (7), age (8), and asthma (9). Despite the many studies on inhaled insulin, limited information is available on the effect of physical activity on the absorption of inhaled insulin. Regular physical activity is an important part of the treatment of diabetes and is recommended to all groups of people with diabetes (10).

Large tidal volume ventilation after dosing leads to increased absorption of inhaled insulin in rabbits (11), and increased serum levels of inhaled insulin have been reported in humans after performance of pulmonary function test maneuvers, which included deep breathing (12). Increased absorption/absorption rate as an effect of exercise is well known for other inhaled substances such as technetium 99m-labeled diethylene triamine penta-acetic acid (13,14), nedocromil sodium (15), and terbutaline (16). In a recent preliminary study in healthy volunteers who exercised after inhalation of insulin via a nebulizer system, we saw clinically relevant effects of exercise (17) and thus warranted further investigations in people with type 1 diabetes who respond differently to exercise than healthy people (18). People with diabetes might perform increased physical activity (exercise) at different time points after dosing, and the impact of timing of exercise on insulin absorption is therefore of interest. Thus, the purpose of this study was to investigate the effect of exercise on the absorp-

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Abbreviations: AUC, area under the curve; GIR, glucose infusion rate; iDMS, insulin diabetes management system; IPAC, International Physical Activity Questionnaire.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tion of inhaled insulin via the AERx iDMS when performed at three clinically relevant time points.

RESEARCH DESIGN AND METHODS

— This study was carried out according to the principles of the Declaration of Helsinki (19) and good clinical practice (20). All subjects gave written informed consent before any study-related activities.

Twenty-three male and female subjects with type 1 diabetes were included in the study. The following were the inclusion criteria: aged between 18 and 65 years (both inclusive), BMI ≤29 kg/m^2, nonsmoker for at least 6 months (nonsmoking status confirmed by negative cotinine test), and normal pulmonary function (defined as forced vital capacity and forced expiratory volume in 1 s >80% and forced expiratory volume in 1 s/forced vital capacity ≥75% of predicted values). Subjects with past or present pulmonary disease were excluded, as were subjects with any clinically significant findings from a cardiopulmonary exercise test performed at screening. This single-center, open-label, randomized, four-period, crossover, isoglycemic clamp study consisted of six visits: a screening visit, 4 dosing days separated by a washout period of 2–15 days, and a follow-up visit.

On separate days, in randomized order, all subjects received four treatments: inhaled human insulin and *1*) no exercise (NOEX group) or exercise starting, *2*) 30 min after dosing (EX30), *3*) exercise starting 120 min after dosing (EX120), and *4*) exercise starting 240 min after dosing (EX240). The time point of 30 min after dosing was chosen as the earliest clinically relevant time of exercise after insulin inhalation, the time point of 240 min after dosing was chosen as a late time point for exercise, while the time point of 120 min after dosing was chosen as an intermediate time point.

The subjects attended each dosing day in the morning in a fasting state and remained fasting and in supine position, except for periods of exercise, during the study day. Subjects on multiple injections of insulin injected their last insulin dose before 8:00 P.M. the day before. Subjects on long-acting insulin analogs were transferred to NPH insulin at least 3 days before each dosing day. Subjects on continuous subcutaneous insulin treatment stopped their insulin infusion upon admission.

A hand or antecubital vein was cannulated and kept in a thermoregulated box (~50°C) for the sampling of arterialized venous blood. An antecubital vein on the contralateral arm was cannulated for the infusion of glucose. A stable plasma glucose level of 130 ± 20 mg/dl (7.2 ± 1.1 mmol/l) was achieved by variable intravenous infusion of human insulin (insulin human [rDNA]; Novo Nordisk, Bagsvaerd, Denmark). From $t = -40$ to -10 min the infusion was kept stable. After, it was tapered (from $t = -10$ to -5 min, reduced by 25%; from -5 to 0 min, reduced to 50% of the stable infusion) then stopped immediately before insulin was inhaled at $t = 0$ min. Venous blood samples for plasma glucose measurements were obtained, on average, every 5–10 min during the experiment, and plasma glucose was measured in duplicate using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Isoglycemia at 130 ± 20 mg/dl (7.2 ± 1.1 mmol/l) was maintained by variable glucose infusion (glucose 10%; Fresenius Kabi, Graz, Austria and Braun Infusomat, Melsungen, Germany).

Blood samples for total serum insulin were drawn in intervals of 5–60 min during the dosing days. To assure accurate estimation of free insulin concentrations, immediate centrifugation of the blood samples and extraction of insulin antibodies by polyethylene glycol precipitation were performed (21). Free plasma human insulin was measured using a commercially available enzyme-linked immunosorbent assay (Dako, Cambridgeshire, U.K.) at Capio Diagnostik (Copenhagen, Denmark).

Dosing

At each visit, the subjects received a dose of 0.19 units/kg inhaled human insulin (1,500 units/ml insulin human inhalation solution, 50 μl/strip; Novo Nordisk) administered via the AERx iDMS (version P3; Novo Nordisk). One unit corresponds to ~1 IU given subcutaneously. The dose was delivered in one or two inhalations, depending on dose. The mass median aerodynamic diameter of the aerosol was 2.4 μm, with a geometric SD of 1.3, measured using an Andersen MK II Cascade impactor (Thermo Scientific, Waltham, MA).

Exercise protocol

At screening, physical activity level was characterized using the International Physical Activity Questionnaire (IPAQ) (22), and a cardiopulmonary exercise test was done to establish each subject's maximal oxygen uptake ($V\text{O}_{2\text{max}}$). The initial workload was 20 W with 15-W increments every minute until exhaustion. During the 3 dosing days with exercise, cycle ergometer exercise at constant workload, corresponding to 50% of $V\text{O}_{2\text{max}}$ (i.e., moderate exercise) (10) with a pedal intensity of 60–80/min, was carried out for 30 min, followed by a 2-min cool-down period at 40 W. Just before start of exercise and every 10 min thereafter, heart rate, ventilation rate, tidal volume, minute ventilation, and Borg rating of relative perceived exertion (23) were recorded.

Safety

Safety assessments included adverse events, pulmonary function tests, physical examination, electrocardiogram, vital signs, and standard laboratory safety parameters.

Statistical methods

The sample size of 21 completers was based on an ability to detect a 20% treatment difference in the area under the curve (AUC) for the free plasma insulin from 30 to 150 min [$\text{AUC}_{\text{ins(30–150 min)}}$], with a two-sided significance level of 5% and a power of 90%.

In all cases, AUC was calculated by means of the trapezoidal rule. $\text{AUC}_{\text{ins(30–150 min)}}$ was transformed with the natural logarithm and analyzed by an ANOVA model including treatment as fixed effect and subject as random effect. The secondary end points [$\text{AUC}_{\text{ins(120–240 min)}}$, $\text{AUC}_{\text{ins(240–360 min)}}$, $\text{AUC}_{\text{ins(0–360 min)}}$, $\text{AUC}_{\text{ins(0–600 min)}}$, C_{max}, t_{max}, λ_z, and mean residence time] were analyzed similar to $\text{AUC}_{\text{ins(30–150 min)}}$. For $\text{AUC}_{\text{ins(30–150 min)}}$ and $\text{AUC}_{\text{ins(120–240 min)}}$, the combined data from the NOEX group and EX240 were used as "no exercise" comparison, as any influence of exercise at 240 min after dosing was irrelevant for the evaluation of the 30- to 150-min as well as the 120- to 240-min time period.

The pharmacodynamic end points [AUC for the glucose infusion rate (GIR): $\text{AUC}_{\text{GIR(30–150 min)}}$, $\text{AUC}_{\text{GIR(120–240 min)}}$, $\text{AUC}_{\text{GIR(240–360 min)}}$, $\text{AUC}_{\text{GIR(0–360 min)}}$, and $\text{AUC}_{\text{GIR(0–600 min)}}$] were calculated and analyzed similar to the corresponding pharmacokinetic end points. Individual GIR profiles were smoothed by a LOESS function, and GIR_{max} and t_{GIRmax} were calculated from smoothed GIR profiles and analyzed similarly to C_{max} and t_{max}.

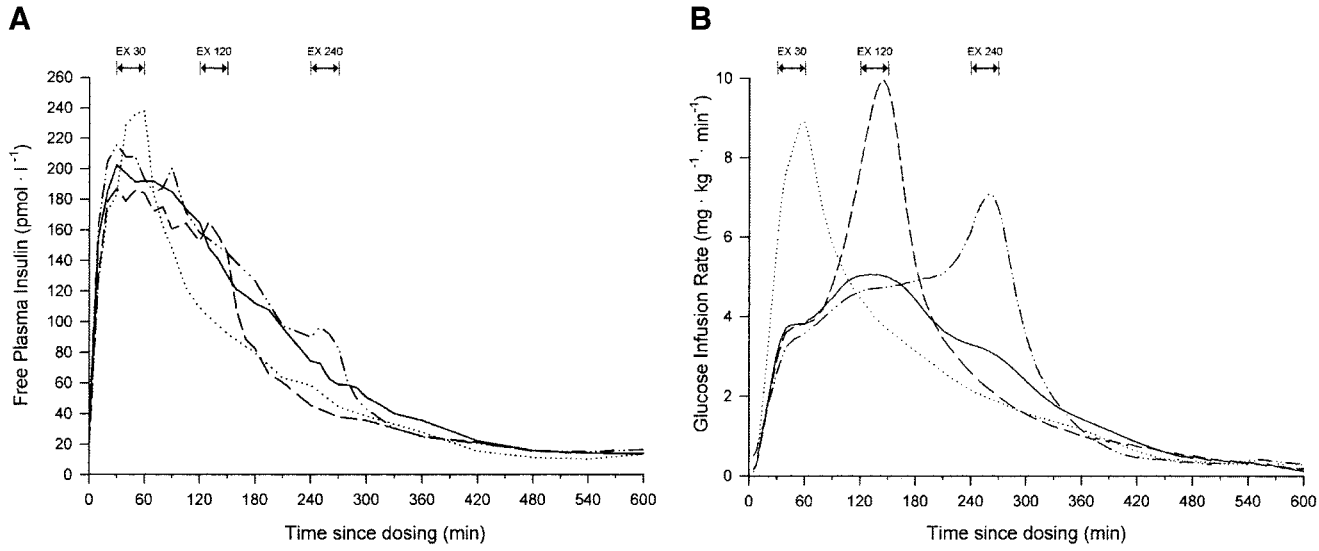

Figure 1—*Mean free plasma insulin concentration curves* (A) *and GIR curves (smoothed means)* (B). *Unbroken line, no exercise; dotted line, EX30; dashed line, EX120; dotted and dashed line, EX240. The three periods of exercise (EX30, EX120, and EX240) are indicated with horizontal arrows at the top of each figure. Note that the estimates of C_{max} and GIR_{max} from Table 1 are more representative, as these are based on the ANOVA model taking into account that C_{max} and GIR_{max} are only normally distributed when the natural logarithm is applied.*

Data from the IPAQ questionnaire were summarized (24) in categories and in metabolic equivalent minutes (MET-min), where MET-min is approximately equivalent to kilocalories for a 60-kg person. A significance level of 5% was used throughout, and all tests were made against the NOEX group.

RESULTS — A total of 29 subjects were screened, and 23 subjects were randomized in the study: 8 women and 15 men, all were Caucasians, all were aged (mean [range]) 34.7 years (21.3–46.4), had BMI 24.5 kg/m^2 (19.8–28.4), had diabetes duration 17.6 years (4.2–40.8), had an A1C 7.8% (6.0–10.2), and all were C-peptide negative. Two subjects were withdrawn; one withdrew due to an adverse event (circulatory collapse during exercise) at the first dosing visit, and one withdrew consent after two dosing visits due to private time schedule issues. Thus, 21 subjects completed the study. All 23 subjects exposed were included in the safety evaluation, while 22 subjects with at least one full free plasma insulin or GIR profile were included in the pharmacokinetic and pharmacodynamic analyses.

The subjects reflected a normal population, with 44% being in the IPAQ "high" activity category, 39% being in the IPAQ "moderate" activity category, and 17% being in the IPAQ "low" activity category and with a $V_{O_{2max}}$ of (means ± SD) 40 ± 7 ml · min^{-1} · kg^{-1} and a total median activity score of 2,457 MET-min/week (range 396–15,039).

Exercise

The physiological response to exercise was reproducible between the 3 exercise days. Mean heart rate increased for all treatments from ~80 beats/min at rest (EX30: 82 ± 13, EX120: 85 ± 20, and EX240: 78 ± 12) to ~130 beats/min during exercise (EX30: 132 ± 21, EX120: 131 ± 21, and EX240: 127 ± 20). The ventilation rate hardly changed from ~16 breath/min (all: 16 ± 5) to ~18 breath/min during exercise (EX30: 19 ± 5, EX120: 18 ± 4, and EX240: 18 ± 5), while tidal volume changed from 0.9 ± 0.4 l (EX30, EX120, and EX240) during rest to 2.0 during exercise (EX30: 2.0 ± 0.6 and EX120 and EX240: 2.0 ± 0.5), leading to a change in minute ventilation from ~13 at rest (EX30 and EX120: 13 ± 5 and EX240 14 ± 6) to ~35 during exercise (EX30 and EX120: 35 ± 11 and EX240: 34 ± 11).

Pharmacokinetic results

The mean plasma insulin concentration profiles are shown in Fig. 1. For all exercise treatments, an increase in the mean plasma insulin was seen at the time of exercise, followed by a sharper decrease. Compared with the NOEX group, no difference in absorption of insulin was seen for EX30 or EX240 from start of exercise to 2 h onwards (Table 1). For EX120, a decrease of 15% in absorption over the first 2 h after the start of exercise was observed ($P = 0.002$; Table 1). Compared with the NOEX group, the overall absorption from 0 to 360 or from 0 to 600 min was decreased by 13% for EX30 ($P < 0.005$ for both) and by 11% for EX120 ($P < 0.01$ for both; Table 1), while no influence was seen for EX240 (Table 1). C_{max} was not significantly influenced by exercise, whereas t_{max} occurred ~22 min earlier for EX30 ($P = 0.041$) compared with the NOEX group (while not significantly influenced for EX120 and EX240). There was no statistical significant effect of exercise on λ_z or on mean residence time.

Pharmacodynamic results

As clearly seen in Fig. 1, the glucose need increased during periods of exercise, with GIR_{max} related to exercise periods (Table 1). Thus, the AUC_{GIR} for the 2 h after start of exercise was increased for all exercise treatment (Table 1). The overall need for glucose over 6 and 10 h [$AUC_{GIR(0-360\ min)}$ and $AUC_{GIR(0-600\ min)}$] was not significantly changed for EX30 compared with the NOEX group (Table 1), while it increased for EX120. For EX240, $AUC_{GIR(0-360\ min)}$ was increased, while the increase for $AUC_{GIR(0-600\ min)}$ did not reach statistical significance ($P = 0.09$).

Safety

A total of seven adverse events were observed in six subjects. None were serious, and none were judged related to the inhaled insulin. Five (nasopharyngitis, tracheobronchitis [after last dosing day], headache [two cases], and orthostatic hypotension) were mild, one (nausea) was moderate, and one (circulatory collapse

Table 1—*Pharmacokinetic and pharmacodynamic end points*

	NOEX	EX30			EX120			EX240		
Treatment	Mean (95% CI)	Mean (95% CI)	Mean ratio (95% CI)	*P*	Mean (95% CI)	Mean ratio (95% CI)	*P*	Mean (95% CI)	Mean ratio (95% CI)	*P*
n	22	21			21			22		
Insulin										
$AUC_{ins(30–150\ min)}$*	17,221 (12,418–23,881)	15,969 (11,458–22,257)	0.93 (0.84–1.02)	NS	—	—	—	—	—	—
$AUC_{ins(120–240\ min)}$*	11,868 (8,736–16,124)	—	—	—	10,092 (7,384–13,793)	0.85 (0.77–0.94)	0.002	—	—	—
$AUC_{ins(240–360\ min)}$	5,094 (3,745–6,930)	—	—	—	—	—	—	5,176 (3,805–7,040)	1.02 (0.86–1.19)	NS
$AUC_{ins(0–360\ min)}$	34,064 (24,904–46,593)	29,668 (21,681–40,598)	0.87 (0.80–0.95)	0.002	30,193 (22,065–41,316)	0.89 (0.81–0.97)	0.008	35,821 (26,188–48,997)	1.05 (0.96–1.15)	NS
$AUC_{ins(0–600\ min)}$	37,624 (27,972–50,608)	32,665 (24,275–43,956)	0.87 (0.80–0.94)	0.001	33,357 (24,789–44,886)	0.89 (0.82–0.96)	0.006	38,869 (28,897–52,282)	1.03 (0.95–1.12)	NS
C_{max}	213 (156–292)	218 (159–299)	1.02 (0.88–1.19)	NS	192 (140–263)	0.90 (0.78–1.04)	NS	209 (153–287)	0.98 (0.85–1.14)	NS
t_{max}	69 (52–92)	47 (35–63)	0.68 (0.47–0.98)	0.041	57 (42–76)	0.82 (0.57–1.19)	NS	61 (46–82)	0.89 (0.62–1.28)	NS
GIR										
$AUC_{GIR(30–150\ min)}$*	436 (360–529)	688 (554–854)	1.58 (1.34–1.86)	0.000	—	—	—	—	—	—
$AUC_{GIR(120–240\ min)}$*	480 (402–573)	—	—	—	696 (569–852)	1.45 (1.24–1.70)	0.000	—	—	—
$AUC_{GIR(240–360\ min)}$	240 (162–355)	—	—	—	—	—	—	410 (277–606)	1.71 (1.09–2.67)	0.019
$AUC_{GIR(0–360\ min)}$	1,093 (913–1,309)	1,207 (1,006–1,448)	1.10 (0.95–1.28)	NS	1,290 (1,075–1,549)	1.18 (1.02–1.37)	0.029	1,288 (1,075–1,542)	1.18 (1.02–1.36)	0.028
$AUC_{GIR(0–600\ min)}$	1,194 (996–1,432)	1,300 (1,082–1,563)	1.09 (0.94–1.26)	NS	1,389 (1,156–1,670)	1.16 (1.00–1.35)	0.049	1,356 (1,131–1,626)	1.14 (0.98–1.32)	NS
GIR_{max}	5.6 (4.7–6.7)	9.0 (7.5–10.8)	1.61 (1.32–1.95)	0.000	9.9 (8.2–11.8)	1.76 (1.45–2.14)	0.000	7.7 (6.5–9.2)	1.38 (1.14–1.68)	0.001
t_{GIRmax}	111 (94–131)	59 (50–70)	0.53 (0.42–0.67)	0.000	143 (120–170)	1.29 (1.02–1.63)	0.034	217 (183–257)	1.96 (1.55–2.46)	0.000

All means are geometric means [exp(Least Squares Means)] based on ANOVA model. All tests are against no exercise. NOEX, no exercise; EX30, exercise starting 30 min after dosing; EX120, exercise starting 120 min after dosing; EX240, exercise starting 240 min after dosing; NS, nonsignificant. Units: all AUC_{ins}, pmol · min^{-1} · l^{-1}; C_{max}, pmol/l; t_{max}, min; all AUC_{GIR}, mg/kg; GIR_{max}, mg · kg^{-1} · min^{-1}; t_{GIRmax}, min. *NOEX is a combination of NOEX and EX240 treatments (i.e., $N = 44$).

during exercise) was severe. The circulatory collapse, which happened during exercise, started 120 min after dosing, was of brief duration, and was judged not to be caused by the inhaled insulin, as the subject had a normal plasma glucose level. The subject fully recovered. There were no clinically relevant changes in any safety parameters.

CONCLUSIONS — This is the first trial investigating the effects of moderate exercise after administration of inhaled insulin in subjects with type 1 diabetes. Exercise is a recommended treatment option in both type 1 and type 2 diabetes for achieving good metabolic control. Therefore, in this study we investigated the effect of exercise at three different time points (30, 120, and 240 min after inhalation). During exercise, an increase in the pharmacokinetic profiles was observed, which was followed by a sharp decline in plasma insulin concentration to below the level of no exercise after stopping exercise. Consequently, compared with no exercise, the absorption over 2 h after the start of exercise was unchanged for exercise 30 and 240 min after dosing, while it was decreased for exercise 120 min after dosing. C_{max} was unchanged by exercise but came earlier for exercise 30 min after dosing. The overall absorption was slightly decreased or unchanged.

These obtained data are in contrast to what has been obtained in a study with terbutaline (16), where an ~50% increase in maximal plasma terbutaline concentration was seen after 30 min moderate exercise starting immediately after dosing, and also in contrast to what we observed in the recent study in healthy volunteers with inhaled human insulin administered via a nebulizer system, where 30 min moderate exercise, starting 30 min after dosing, led to increased C_{max} and increased insulin absorption during the 2 h after start of exercise (17). For later time points of exercise, there are, to our knowledge, no previous studies with which to compare.

The exercise setup was identical, and the physiological effect of exercise (including ventilation) was comparable between the two studies. Thus, an explanation must be found in other parameters. In observational and experimental studies, an association between diabetes and reduced lung function (25–29), as well as reduced lung diffusion response to exercise (30), has been found. This change could potentially be a part of the explanation for the difference between this study and the previous study (17). Moreover, in the present study, the insulin dose was delivered with the AERx iDMS in one or two inhalations with smaller particles, whereas in the previous study the dose was delivered over 23 voluntary deep breaths by a nebulizer system, which provided a larger particle size (17). This might lead to a difference in deposition, which might influence absorption. However, a recent study (31) with technetium 99m-labeled diethylene triamine penta-acetic acid has shown that deposition might not affect absorption as much as previously anticipated, suggesting that other mechanisms might be involved as well.

Another unexpected finding is decreased overall insulin absorption after exercise. This could either be explained by less available insulin in the lung for absorption, less absorbed insulin, or increased elimination in the blood. As the insulin is already deposited for awhile in the deep lung at the time of exercise, it is unlikely that insulin is exhaled. Another speculation is whether exercise leads to increased degradation of insulin in the lung by increased macrophage activity or increased mucociliary clearance, as has been seen with centrally deposited albumin (32). However, this has not been observed for albumin delivered to the deep lung (33). No difference was found in the terminal absorption rate (represented by the terminal elimination rate, as the absorption is the rate-limiting factor for disappearance of insulin from plasma [flip-flop situation]) or in the mean residence time; thus, there is no indication of a general effect on the absorption rate or elimination. All in all, this finding of decreased absorption remains unexplained and needs to be investigated in future studies.

In general, the pharmacodynamic results supported the pharmacokinetic findings. In each of the exercise intervals, the infusion rate of glucose increased as expected, reflecting a combined effect of the insulin absorption and exercise, followed by a decrease, in line with the concomitant decrease in insulin. For exercise 240 min after dosing, the glucose need was higher than for no exercise, probably reflecting only the exercise itself, making it possible to quantify the glucose need during 30 min moderate cycle exercise to ~170 mg/kg (i.e., ~12 g glucose for a 70-kg person), which is in line with the general recommendations for people with diabetes (34).

The inhaled insulin was well tolerated by all subjects. One person experienced a circulatory collapse, which was considered unlikely to be caused by the insulin. However, although the used dose was of usual clinical sizes, insulin is known to cause vasodilatory effects (35,36), which might have contributed.

The physical activity level in this study reflects daily life activities, such as biking to work at moderate pace and similar. No conclusions can be drawn about higher levels or longer periods of exercise. This would need to be investigated. Due to the number of acceptable clamps per subject, it was unfortunately not possible to include subcutaneous treatment arms. Thus, as no direct comparison within the study was feasible, it is not possible to directly compare with the effect of exercise on subcutaneous regular human insulin or a rapid-acting analog. However, the relatively small changes in the pharmacokinetics support the use of insulin in connection with exercise with similar precautions as for subcutaneous insulin. Only patients performing exercise early after dosing should be aware of the faster maximal insulin concentration at this time point of exercise. This present study also illustrates the well-known increased metabolic effect of exercise in itself and supports the need for either extra carbohydrate intake or reduction in insulin dose in connection with exercise. The variability observed confirms the need for frequent blood glucose measurements in relation to exercise, at least until the person is aware of his/her own response to the new insulin regimen and exercise.

In summary, 30 min moderate exercise at 30, 120, or 240 min after dosing of inhaled human insulin led to *1*) unchanged or decreased absorption over the first 2 h, *2*) unchanged or decreased overall absorption, and *3*) unchanged maximal insulin concentration compared with no exercise. Thus, individuals using inhaled human insulin via the AERx iDMS can adjust their meal-related insulin dose in connection with increased physical activity as usual. If increasing physical activity early after inhalation of insulin, the person should be aware that the maximal effect that might come earlier than usual. Until the person is aware of his/her response to inhaled insulin in relation to increased physical activity, increased caution and glucose monitoring are warranted in connection with exercise.

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